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Hyperlipidemia: A risk factor for chronic allograft dysfunction

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Hyperlipidemia: A risk factor for chronic allograft dysfunction. While the early results of renal transplantation have improved in the last years, but the long-term allograft survival have not improved to the same extent. The major cause of these graft losses is chronic allograft dysfunction (CAD). The pathogenesis of CAD is complex and results from a interaction of immune and nonimmune factors. Between these non-immunological related factors there are two cardiovascular risk factors, hypertension and especially hyperlipidemia, that have been implicated in the development and progression of CAD. Lipid profile abnormalities are very prevalent in renal transplant patients. In last years several authors have reported an association between different lipid profile alterations and CAD. We conducted an observational study in our group to determine the relationship between different lipid disturbances and CAD. The hypertriglyceridemia and the Lp(a) >30 mg/dL before and after transplantation were, between the lipid abnormalities, the two independent risk factors for CAD in a multivarite analysis.

With the introduction of new immunosuppressive drugs, the early results of renal transplantation have dramatically improved. However, these have not been paralleled by a similar improvement in long-term allograft survival. The number of functioning grafts declines after the first year, and, excluding cases of death with functioning grafts, the major cause of these graft losses is chronic allograft dysfunction (CAD) [1, 2].

CAD has been defined as a progressive functional deterioration of the transplanted kidney in the absence of other causes of graft disease [3]. The clinical diagnosis of CAD is suggested by slowly rising plasma creatinine concentrations, increasing proteinuria, and worsening hypertension [4]. A histological classification of the severity of CAD, called the Banff classification, has been formulated [5].

The pathogenesis of CAD is complex and only partially understood, and has been considered to result from an interaction of various immune (sometimes historically called "chronic rejection") and nonimmune factors implicated in its development and progression. For the immune factors, there is acute rejection, but not all forms have the same impact on CAD. The risk is increased in severe, late, or recurrent episodes [6, 7], and is affected by the HLA system, especially in cases with HLA-DR locus mismatches [6]. In the same way, it has been suggested that the utilization of low-maintenance doses of immunosuppressants, especially cyclosporine A (CsA), can lead to a state of sub-optimal immunosuppression that forms an additional risk factor for CAD [8].

Nonimmune factors may be involved in CAD pathogenesis related to a diminished functional mass of the renal graft. This diminution can be caused by disproportionate size differences between donor and receptor, and by differences in donor age, gender, and ethnicity. In addition, structural and functional damage produced by prolonged graft ischemia, surgical manipulation, and delayed graft function, that is the clinical manifestation of ischemia–reperfusion injury could contribute also. The decrease in nephron number could lead to hyperfiltration in remnant nephrons, leading to progressive renal failure [9]. Other factors, such as prolonged immunosuppressant toxicity (especially for CsA and Tacrolimus), and cardiovascular risk factors such as hypertension and especially hyperlipidemia, could contribute to renal injury and the appearance of CAD. Because one of the hallmarks of CAD is a vascular lesion characterized by intimal proliferation and luminal narrowing that resembles the atherosclerotic disease, many investigators have proposed a role for cardiovascular risk factors in the pathogenesis and progression of CAD. Hypertension after transplantation has indeed been linked with CAD [10] when it is also present before transplantation [11].

ROLE OF LIPID ABNORMALITIES IN CHRONIC ALLOGRAFT DYSFUNCTION

Renal insufficiency is often accompanied by hyperlipidemia, which worsens in severity as one approaches ESRD. After successful renal transplantation, however, there is no assurance of the remission of dyslipidemia. Indeed, lipid profile changes and hyperlipidemia are found in 16% to 72% of patients, depending on the time serum lipids are examined after transplantation, and by which factors they are influenced [12]. Lipid abnormali-

Key words: renal transplantation, graft loss, lipid profile, hypertriglyceridemia.

ties in transplanted patients have been associated with multiple factors: age, pretransplant serum lipids [13, 14], body weight [15], allograft dysfunction [13], hyperinsulinemia and diabetes [16], antihypertensive therapy [16], prednisone dosage [16], and cyclosporine dosage and blood levels [17].

The renal transplant population frequently displays elevations in total cholesterol, LDL cholesterol, triglycerides, apolipoprotein B (Apo B), and lipoprotein(a) or Lp(a). There may also be diminution in HDL, and qualitative alterations in lipoproteins such as the increased susceptibility of LDL to oxidation. Thus, the lipid profile in renal transplant patients may show an atherogenic pattern linked with the appearance of the cardiovascular complications that are the most frequent causes of death in this population [18]. In this setting, it is important to note that vascular lesions in systemic atherosclerosis share similarities with lesions seen in CAD. Macrophages, foam cells, lipoproteins, T cells, and proliferating smooth muscle cells can be demonstrated in the vascular wall of kidneys with CAD lesions [18, 19]. These observations have led to several studies on the role of lipid disorders in CAD. In animal models it has been demonstrated that a high cholesterol diet accelerates proliferative vascular changes in graft vessels [20]. Although some reports have focused mainly on the role of elevation in serum cholesterol, particularly on its quantitative abnormalities, recent studies also show that there may be qualitative alterations to lipoproteins that can play a central role in the pathogenesis of CAD. An enrichment of triglycerides in VLDL and LDL lipoproteins has been reported in renal transplant patients. These small, dense LDL particles with reduced receptor-specific uptake [21] show increased susceptibility to oxidative modification in the presence of inflammation when there is an excess of production of reactive oxygen metabolites, as in allografts. Tanabe et al have demonstrated oxidized LDLs, using monoclonal antibodies in arteries of grafts of patients with hypercholesterolemia and with CAD [22]. It has been reported that patients with CAD have increased levels of malondialdehyde, an end product of lipid peroxidation, and low levels of the antioxidants vitamin E and superoxide dismutase compared with patients with stable graft function, and with controls [23].

There is experimental evidence that oxidatively modified LDL may be cytotoxic for mesangial cells and may also have adverse effects on extracellular matrix components [24]. The pathogenic mechanisms by which the oxidized LDL could contribute to the development of CAD are as follows. The oxidized LDL induces the activation of T lymphocytes and the expression of adhesion molecules and class II MHC antigens. It also induces chemoattraction of monocytes and their differentiation into macrophages, and enhances their adhesion to the endothelial surface, probably by inducing the expression of the adhesion molecules ICAM 1 and ELAM 1. These activated macrophages are present in chronically rejected allografts and express TGF-β receptors. Oxidized LDL is the ligand for scavenger receptors on macrophages, which are then converted into foam cells. It also increases the expression of PDGF receptors in smooth muscle cells that can be converted to fibroblast-like cells with a matrix-producing capacity [25]. On the other hand, a diminution in nitric oxide production has also been reported [12]. All these effects lead to the fibrosis of the intimal vessels that is characteristic of CAD.

Coagulation abnormalities have also been related to CAD. These include impaired fibrinolysis with increased PAI-1 levels, the synthesis of which is related in a dose-dependent way to oxidized LDL levels [12]. Elevated levels of fibrinogen have also been described [26, 27].

Several reports have pointed toward a link between different lipid profile alterations and CAD.

TOTAL CHOLESTEROL AND TRIGLYCERIDE LEVELS

Elevated cholesterol levels have been implicated in the aggravation of vascular lesions in experimental models of CAD [20]. Several clinical studies have also reported an association between cholesterol levels and different indicators of CAD.

Dimény et al have reported that 42 patients with CAD presented with higher cholesterol and triglyceride levels than did 42 controls without CAD at a similar time after transplantation [28]. In another study by the same group of 56 patients (28 with biopsy-proven CAD and 28 with stable renal function), the pretransplant cholesterol levels were associated with a higher chronic damage score and worse graft function at six months after transplantation. There was also an association between increased cholesterol and triglyceride levels at six months and parameters indicating graft dysfunction at the same time [13]. In both studies, however, patients with high cholesterol levels had more frequent acute rejection episodes, but no multivariate analysis was performed. In this context, it is difficult to differentiate the effects of hypercholesterolemia alone. In another series of 151 patients, they found that high cholesterol levels before transplant and at six months after transplantation were associated with poor graft function at two years [29].

Wissing et al studied 772 renal transplant patients and reported that hypercholesterolemia was an independent risk factor for kidney graft loss by chronic rejection in male patients with previous acute rejection [30]. Roodnat et al agreed with this observation in a study carried out on 676 patients in whom cholesterol was an independent predictor of graft outcome [31]. Serón and colleagues have published that the total serum cholesterol before transplantation was the only predictor of CAD with

Table 1. Association between the studied parameters and the risk of developing CAD, using multiple logistic regression analysis: General characteristics and lipid metabolism before transplant

Factor	OR	95% CI	*P* value
Age	0.89	(0.83–0.98)	0.006
Gender			
Male	1	(0.17–3.07)	0.680
Female	0.74		
Diabetes			
No	1	(0.98–2.95)	0.477
Yes	0.53		
HDL			
<45 mg/dL	1	(0.04–0.73)	0.017
>45 mg/dL	0.17		
Lp(a)			
<30 mg/dL	1	(1.19–1.83)	0.013
>30 mg/dL	1.40		
Triglycerides			
<200 mg/dL	1	(1.05–1.98)	0.048
>200 mg/dL	1.27		
VLDL			
<25 mg/dL	1	(1.00–1.22)	0.034
>25 mg/dL	1.10		

Abbreviations are: CAD, chronic allograft dysfunction; HDL, high density lipoprotein; Lp(a), lipoprotein(a); VLDL, very low density lipoprotein; OR, odds ratio; CI, confidence interval.

Table 2. Association between the studied parameters and the risk of developing CAD, using multiple logistic regression analysis: General characteristics and lipid metabolism after transplantation

Factor	OR	95% CI	*P* value
Age	0.81	(0.70–0.93)	0.004
Gender			
Male	1	(0.02–1.98)	0.182
Female	0.23		
Diabetes			
No	1	(0.01–4.41)	0.368
Yes	0.28		
Acute rejection			
No	1	(0.07–30.03)	0.794
Yes	1.49		
HDL, 1 year			
<45 mg/dL	1	(0.01–0.22)	0.006
>45 mg/dL	0.10		
Lp(a), 1 year			
<30 mg/dL	1	(1.17–1.65)	0.015
>30 mg/dL	1.50		
Cholesterol, 6 months			
<240 mg/dL	1	(0.99–1.39)	0.057
>240 mg/dL	1.23		
Triglycerides, 1 year			
<200 mg/dL	1	(2.00–257.69)	0.011
>200 mg/dL	22.71		
Lipid-lowering therapy			
No	1	(0.51–40.91)	0.221
Yes	4.13		
CsA dosage, 2 years			
<5 mg/kg	1	(0.09–0.57)	0.013
>5 mg/kg	0.07		

transplant vasculopathy in 280 protocol biopsies at three months [32]. Isoniemi et al reported that patients with a graft loss at four years after transplant had higher cholesterol and triglyceride levels at two years following transplant, but multivariate analysis failed to substantiate either factor as predictors of graft outcome [33]. Fernandez-Miranda et al have described the role of triglycerides as independent risk factors for CAD in a case-controlled study of 60 patients [27], as have Guijarro et al [34] and Massy et al for 706 renal transplant patients [35]. However, there are other studies that have failed to establish any relationship between hyperlipidemia and CAD in two series of 46 [36] and 450 patients[37], respectively.

Lipoproteins and Lp(a)

Some reports have addressed the role of different lipoproteins in the development of CAD. Isoniemi et al reported a positive correlation between LDL and CAD [33]. Dimény et al reported a similar positive correlation between LDL and VLDL with CAD, and also an inverse correlation between HDL and indicators of chronic damage [13, 29]. By contrast, Guijarro et al did not find any correlation with the levels of LDL; however, HDL levels below 35 mg/dl tended to be associated with an increased risk of CAD [34]. Bosmans et al reported that an HDL level of less than 47 mg/dL was a risk factor for the functional and morphological outcome of the graft at 18 months after transplant and was inversely associated with the interstitial accumulation of oxidized LDL and consequently with the development of interstitial fibrosis [38].

The Lp(a) levels were not associated with CAD in the report of Fernandez-Miranda et al [27].

ASSOCIATION BETWEEN HYPERLIPIDEMIA AND CAD: A SINGLE CENTER EXPERIENCE

To determine the relationship between lipid disturbances and CAD, we conducted a study on 77 kidney transplant patients. All were transplanted in our unit during a 14-month period, and we followed them from transplantation until four years later. The lipid profile was determined before, at six months, and annually after transplantation until the end of the study. Other clinical and biochemical variables were also studied at yearly intervals. During the follow-up 19 patients were diagnosed with CAD. Statistical analysis with multiple logistic regression models were fitted to estimate the risk (OR) of CAD associated with each variable.

Multivariate analysis shows that, between the pretransplant parameters, the independent risk factors for CAD were: hypertriglyceridemia, VLDL >25 mg/dL, and Lp(a) >30 mg/dL (Table 1). The post-transplant parameters that remained independent risk factors for CAD were hypertriglyceridemia and Lp(a) >30 mg/dL at one year. The presence of HDL >45 mg/dL at one year was related with a decreased risk of CAD. Between the general parameters, the dosage of CsA >5 mg/kg at two years and the patient age were also related with a decreased risk (Table 2). We failed to find any relationship between cholesterol and CAD. Although this was significant in univariate analysis, it lost significance in multi-

variate analysis, probably because of two strong predictors: triglycerides and Lp(a). Our results agree with other reports and with Fernandez-Miranda et al [27] and Guijarro et al [34] on the role of triglycerides as an independent risk factor for CAD. The last authors have also encountered an inverse relationship between HDL levels and CAD, but in their report the relationship was not independent of triglycerides as in our series of patients. One of the most interesting findings is that the pretransplant lipid disturbances in triglycerides and Lp(a) are risk factors for the appearance of CAD. These observations could help indicate those patients at greater risk for future graft dysfunction.

THERAPEUTIC/PREVENTIVE APPROACHES TO CAD

The management of CAD remains one of the major challenges facing transplant nephrologists. The approaches to protect the allografted kidney in the long term include immune and nonimmune interventions.

OPTIMIZING IMMUNOSUPPRESSIVE STRATEGIES

Current immunosuppressive regimens, though they are very effective in controlling acute rejection, appear of limited value in CAD. There is no doubt that CsA has contributed to improvements for short-term and medium-term graft outcomes, but its impact on long-term graft survival is more questionable in results obtained from a large series [39]. Another new calcineurin inhibitor, Tacrolimus, could have a potential benefit for long-term graft survival. It is also possible that mycophenolate mofetil (MMF) can reduce the risk of CAD. There is experimental evidence of this in rats. There is also experimental evidence in animal models that rapamycin, a new immunosuppressant macrolide, could help prevent vascular disease, but this needs to be explored in clinical trials.

INTERVENTIONS TO CONTROL NONIMMUNOLOGIC EVENTS

Low protein diet

There is some evidence of a potential beneficial effect of dietary protein restriction [40]. However, these findings should be considered with caution because the studies are small and short-term. Additional trials are needed before protein restriction can be recommended as a treatment option.

Antihypertensive medications

It is recognized that hypertension is associated with a poorer outcome after renal transplantation. Moreover, a significant negative correlation was found between renal allograft survival and the degree of hypertension in patients with CAD [7]. Angiotensin-converting enzyme (ACE) inhibitors have been suggested as therapeutic alternatives to treat post-transplant hypertension. Blockade of the rennin-angiotensin system with ACE inhibitors or angiotensin II receptor antagonists reduces urinary protein excretion and protects against glomerulosclerosis. One short-term study found that lisinopril decreased protein excretion in transplant recipients in patients with hypertension and proteinuria without adverse effects [41].

LIPID-LOWERING AGENTS

Drug treatment is necessary in many renal transplant patients to control lipid disorders because dyslipidemia is not particularly responsive to modifications in dietary fat intake. The HMG-CoA reductase inhibitors (statins) are the most effective agents in reducing total lipids and LDL cholesterol, and also the levels of oxidized LDL [18, 42]. In those few patients in whom hypertriglyceridemia and low HDL cholesterol are the leading lipid abnormalities, the fibric acid derivates, especially genfibrozil, are the agents of choice. On the other hand, statins have direct effects on smooth muscle and mesangial cell proliferation and increase the synthesis of nitric oxide [42]. Indeed, there is growing evidence that they could also have immunosuppressive properties. A study of 97 heart transplant patients treated with pravastatin showed reductions in the degree of intimal hyperplasia in coronary arteries [43]. If the pathogenesis of allograft vascular pathology in renal and cardiac transplant recipients is similar, then statins may also hold promise for preventing or treating CAD, and there are ongoing studies on the use of these drugs in renal transplant patients. Although no conclusive data exist proving that statins directly inhibit the development of CAD, it is clear that at present a therapeutic approach for CAD could be the combination of lipid-lowering drugs and the selective use of antihypertensive and immunosuppressive agents, which minor deleterious effects on lipoprotein metabolism.

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